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Does seasonal allergic rhinitis increase sensitivity to ammonia exposure?

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ABSTRACT

Allergic inflammation in the upper airways represents a wide-spread health issue: Little is known about whether it increases sensitivity to airborne chemicals thereby challenging established exposure limits that neglect such differences in susceptibility. To investigate the role of pre-existing allergic inflammation, 19 subjects with seasonal allergic rhinitis (SAR) and 18 control subjects with low risk of sensitization were exposed for 4 h to ammonia in two concentrations (cross-over design): 2.5 ppm (odor threshold) and 0–40 ppm (occupational exposure limit: 20 ppm TWA). Prior to the whole-body exposure, it was confirmed that subjects with SAR showed persistent inflammation outside the pollen season as indicated by increased exhaled nitric oxide and total immunoglobulin E in serum compared to controls. Despite concentration-dependent increases in chemosensory perceptions and acute symptoms, SAR status did not modulate subjective effects of exposure. Moreover, SAR status did not affect the investigated physiological endpoints of sensory irritation: While eye-blink recordings confirmed weak ocular irritation properties of ammonia at 0–40 ppm, this effect was not enhanced in SAR subjects compared to controls. Irrespective of SAR status, exposure to 0–40 ppm ammonia did not result in a cortisol stress response, objective nasal obstruction as measured with anterior active rhinomanometry, or an inflammatory response as indexed by substance P, tumor-necrosis-factor α, and high-mobility-group protein 1 in nasal lavage fluid. At least for the malodorous compound ammonia, these results do not support the hypothesis that SAR enhances chemosensory effects in response to local irritants. Before generalizing this finding, more compounds as well as sensitization to perennial allergens need to be investigated.

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1. Introduction

Seasonal allergic rhinitis (SAR) is a wide-spread health issue in Western countries which affects about 10–20% of the population in a given year (Dykewicz and Hamilos, 2010). It is mediated by the recognition of allergens such as grass pollen by specific immunoglobulin E (IgE) antibodies in sensitized individuals (type I hypersensitivity) leading to the rapid release of inflammatory mediators such as histamine (Greiner et al., 2011). These mediators cause the typical nasal and ocular symptoms associated with SAR such as sneezing, rhinorrhoea, and eye watering.

In a recently published review, Shusterman (2014) argued that a pre-existing inflammation in the upper airways as found in individuals with SAR confers enhanced upper airway sensitivity to air pollutants. Compounds such as ammonia are major contributors to odor annoyance in the environment and at industrial workplaces (Blanes-Vidal et al., 2012; Ihrig et al., 2006). Moreover, exposure to most of these air pollutants in higher concentrations can also cause sensory irritation by activating trigeminal free nerve endings located in the nasal cavity and the eyes (Hummel and Livermore, 2002). This is associated with neurogenic reflexes (e.g. release of substance P, see Chiu et al., 2012) and increased nasal congestion (Shusterman, 2016).

In a series of studies Shusterman and colleagues showed that individuals with SAR indeed exhibit lower lateralization thresholds for irritating *n*-propanol (Shusterman, 2007; Shusterman

et al., 2003a) and an augmented nasal congestive response after exposure to chlorine gas and acetic acid compared to healthy controls (Shusterman et al., 2003b, 2005, 1998). These results are underpinned by electrophysiological evidence showing that higher symptom scores in allergic rhinitis are linked to shorter latencies of event-related potentials in response to nasal CO_2 stimulation (Doerfler et al., 2006).

In line with this, about 40% of individuals with SAR report enhanced sensitivity to non-allergic triggers such as odorous and irritating chemicals (Shusterman and Murphy, 2007). A recent epidemiologic study indicates that even innocuous perfume odors may cause exaggerated reactions in individuals with SAR (Claeson et al., 2016). This suggests that individuals with SAR may be especially susceptible to occupational and environmental chemical exposures compared to individuals without SAR.

Ovalbumin (OVA) sensitized rodent models (Yiamouyiannis et al., 1999) have been used to mimic allergen-related sensitization of humans as indicated by an increased serum IgE level in these animals. Based on these animal models enhanced responses to acrolein and acetic acid could be confirmed in sensitized animals (Morris et al., 2003). However, differences between the two compounds and the two investigated endpoints were shown. For both compounds the sensory response measured as reduction in respiratory rate (RD_{50}-like readout) was generally increased in the OVA-sensitized animals. In contrast, only the airway obstructive response to acetic acid was increased in these animals. Here the duration of the sensitization which is positively associated with its severity was an important factor. Thus, these animal studies as well as the aforementioned epidemiological studies suggest that health based exposure limits for airborne chemicals need to consider inter-individual variability in SAR status (e.g. Brüning et al., 2014).

However, before such a step is taken, a wider range of compounds needs to be tested under controlled but natural breathing conditions (compare Shusterman, 2016). While Shusterman and colleagues used concentrations of chlorine gas and acetic acid that corresponded to (U.S.) short-term exposure limits in their studies (Shusterman et al., 2003b, 2005, 1998), the exposures were restricted to 15 min. Moreover, only a single physiological endpoint, namely objective nasal obstruction, was assessed. To explore the chemosensory effects of acute exposures to local irritants other physiological endpoints such as eye-blink frequency (Kiesswetter et al., 2005) or concentrations of nasal neuropeptides (van Thriel et al., 2003) might be considered more sensitive markers of relevant sensory irritation processes (Brüning et al., 2014).

Therefore, we tested the hypothesis of enhanced sensitivity to airborne chemicals in SAR during an experimental 4 h whole-body exposure to ammonia: In response to concentrations of ammonia at the occupational limit and at the odor threshold (i.e. two conditions in a cross-over design) diverse physiological and subjective effects were assessed in subjects with SAR and control subjects with a low risk of sensitization to seasonal allergens (multilevel approach, see Kleinbeck et al., 2008).

Ammonia was selected as a test substance (a) due to its ubiquitous potential for exposure in daily life (e.g. use in household cleaning products), (b) due to its psychophysically well-established odor threshold (Smeets et al., 2007) and (c) due to its strong impact on reported chemosensory perceptions and symptoms (Ihrig et al., 2006; Pacharra et al., 2016a,d). Accordingly, it was expected that ammonia would concentration dependently impact chemosensory mediated endpoints with stronger effects for SAR compared to control subjects (compare Shusterman, 2014). As in previous studies on the effects of SAR, all subjects were tested outside the pollen season (Shusterman et al., 2003b, 2005, 1998): This was done to avoid confounding effects of pre-existing acute nasal congestion.

Table 1

Descriptive data of the subjects with seasonal allergic rhinitis (SAR) and controls (means and standard deviations shown).

	controls	SAR	[a]p-value
women/men, *n*	10/8	9/10	ns
age, *years*	23.6 ± 2.5	25.1 ± 3.9	ns
FEV1 (% of predicted)	98.9 ± 10.8	98.2 ± 9.7	ns
odor identification ability	12.9 ± 1.4	13.3 ± 1.6	ns
FeNO, *ppb*	15.3 ± 6.2	38.5 ± 31.2	.004
total immunoglobulin E, *kU/l*	39.9 ± 45.2	169.8 ± 137.0	.001
trait anxiety	33.8 ± 8.3	39.9 ± 9.4	.043
self-reported general sensitivity	28.1 ± 12.8	39.8 ± 17.6	.026
self-reported trigeminal mediated sensitivity	4.7 ± 5.9	7.7 ± 7.7	ns

FEV1 = volume that was exhaled during the first second of forced expiration; *FeNO* = fraction of exhaled nitric oxide.

[a] Independent samples *t*-test. ns = not significant.

2. Material and methods

2.1. Subjects

Forty-eight non-smoking subjects were recruited for the study. Exclusion criteria were pregnancy, history of asthma and chronic diseases (in addition to SAR), current use of antihistamines, nasal steroids, and decongestants. For the purpose of this study, confirmed SAR was defined as (a) a history of seasonally occurring symptoms which are in accordance with allergic rhinitis (Shusterman et al., 2003b, 2005, 1998), (b) a report of a medical diagnosis of seasonal allergic rhinitis in the past, and (c) a concentration of allergen-specific IgE in serum consistent with reported allergens (77.3% of subjects: grass pollen; 22.7%: tree or hazel pollen) and indicative of allergic rhinitis (>.35 AU/ml, see e.g. Bokanovic et al., 2013; Hatzler et al., 2012). Subjects who reported (a) no history seasonally occurring symptoms which are in accordance with allergic rhinitis and (b) no medical diagnosis of seasonal allergic rhinitis in the past were considered at low risk for sensitization to seasonal allergens. For the purpose of this study, these subjects were considered as control subjects.

Before participating in the study, all subjects passed a health check by an occupational physician on a separate test day (Kobald et al., 2015). The standardized physiological and psychological assessment included (a) a lung function test (VitaloGraph, Hamburg, Germany), (b) an olfactory function test (Sniffin' Sticks identification test, Burghart, Wedel, Germany), (c) a measurement of fractional exhaled nitric oxide (FeNO; NIOX Mino, Aerocrine, Sweden, see ATS/ERS, 2005), (d) an analysis of total IgE in serum from venomous blood samples (DIN EN ISO 15189 certified laboratory), and (e) questionnaires on trait anxiety (Spielberger, 1983) and self-reported sensitivity (Kiesswetter et al., 1999). Trait anxiety and self-reported sensitivity constitute relevant inter-individual differences in chemosensory-mediated adverse effects (Pacharra et al., 2016b).

Eleven subjects were omitted from data analysis: Five subjects were excluded due to missed test days, three subjects due to technical problems during the recording of eye blinks, and three subjects due to technical problems during the nasal fluid sampling. Descriptive data for the remaining 37 subjects is presented in Table 1.

As can be seen in Table 1, the control and the SAR group did not differ with respect to gender ratio, age, lung function, odor identification ability, and self-reported trigeminal mediated sensitivity. However, subjects with SAR had higher FeNO and a higher total IgE concentration in serum compared to controls. Moreover, SAR subjects reported stronger general sensitivity and trait anxiety than controls.